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Reticulated Pd(II)/Cu(I) cyclodextrin complexes as recyclable green catalyst for Sonogashira alkynylation

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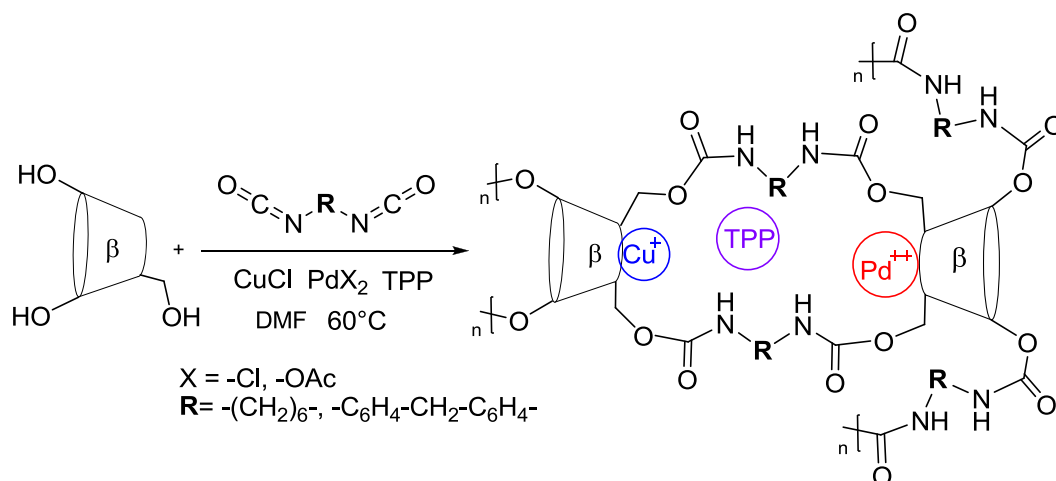
A Pd/Cu loaded polymeric cyclodextrin catalyst was easily prepared via *in situ* reticulation with diisocyanates under sonochemical conditions. Excellent yields were observed for Sonogashira reactions carried out in water and glycerol and the catalyst could easily be recovered and reused three times without a significant loss in catalytic activity.

The Sonogashira reaction, namely the alkynylation of aryl or vinyl halides with terminal alkynes, is a powerful tool for the synthesis of substituted acetylenes¹. It is one of the most common Pd-catalyzed C-C cross-couplings to be exploited in the synthesis of fine chemicals², heterocycles³, natural products and pharmaceuticals⁴. The need to overcome the use of co-catalysts, toxic and high-boiling solvents and the residual amount of ligands and metal in the products has, in recent years, led to greener Sonogashira protocols which use copper-free methods⁵, alternative solvents⁶ and recyclable heterogeneous/homogeneous Pd catalysts⁷. A wide range of supported Pd catalysts (such as Pd/C)⁵ and Pd nanoparticles⁸ have been tested in different reaction media⁹. Moreover the use of co-catalysts, typically two metals (Pd and Cu), has been widely investigated with the aim of reducing the total catalyst load¹⁰. In recent years, functionalized cyclodextrins (CDs) have emerged as possible environmentally friendly supports for Pd nanoparticles⁶ as they improve reaction rates and yields. A protocol involving water soluble β CD-capped Pd nanoparticles under ligand-free and copper-free conditions⁷ paved the way for new investigations in this field. β CD has proven itself to be a good support for metal nanoparticles^{11,12} and many papers have shown its efficacy in the catalysis of different reactions in water^{13,14}. Glycerol has also been the subject of several investigations in its role as a green cost effective solvent for organic reactions^{15,16}. In this study we describe the preparation of a new Pd(II)/Cu(I) loaded polymeric CD catalyst (poly- β CD/Pd/Cu) and its application in the Sonogashira reaction. Besides the classic couplings carried out in DMF, several trials were performed in glycerol and water, two benign media in which the new polymeric catalyst can be easily recycled. This green approach may be of pivotal importance in the field of modern sustainable synthetic process design.

We have previously shown that Pd-catalysed couplings can be performed in the presence of solid catalysts such as cross-linked chitosan/Pd(II)¹⁸. An easy and reproducible one-pot sonochemical CDs reticulation¹⁹ has now been employed to obtain poly- β CD/Pd/Cu nanoparticles (Scheme 1). To this end, the cross-linking agent was slowly added under intense sonication to the reacting mixture containing β -

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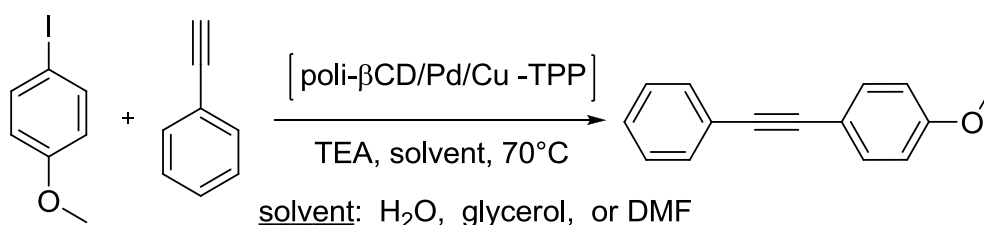
CD, Pd(II) and Cu(I) salts, and when appropriate triphenylphosphine (TPP). Hexamethylene diisocyanate (HDI) and methylene diphenyl diisocyanate (MDI) were tested as cross-linkers. The reaction mixture was thermostatted at 60 °C and after sonication for 30 min an opaque compact gel was obtained. The particles size of the catalyst powder measured by photon correlation spectroscopy (Coulter) after dispersion in water was in a range of 700-1100 nm.



Scheme 1. Preparation of poly-βCD/Pd/Cu nanoparticles.

The average content of metal in the different poly-βCD/Pd/Cu nanoparticles analyzed by ICP was 0.65% for Pd, and 0.90% for

Cu. Although Pd and Cu cations as well as TPP should be tightly embedded in the CD-polymer net, the catalytic activity is not only maintained but even enhanced. In a preliminary set of experiments of Sonogashira coupling the poly-βCD/Pd/Cu nanoparticles did not contain TPP, which was added as a free molecule together with the base (TEA). Phenylacetylene and *p*-iodoanisole were chosen as model substrates for this investigation (Scheme 2).



Scheme 2. Reaction conditions and solvents.

The simple mixture of Pd(II) and Cu(I) salts was compared with several types of poly-βCD/Pd/Cu nanoparticles with the aim of selecting the best catalytic system (Table 1). This was done by varying the salt anion and the cross-linker (MDI or HDI). The role of TPP was also studied.

Table1. Reaction yields with different catalysts^a.

Entry	Catalyst (2%)	Yield (%) ^b
1	Pd(OAc) ₂ , CuCl	57
2	Pd(OAc) ₂ , CuCl, + free TPP	78
3	PdCl ₂ , CuCl	69
4	PdCl ₂ , CuCl, + free TPP	72
5	MDI poly-βCD Pd(OAc) ₂ /CuCl	100
6	HDI poly-βCD Pd(OAc) ₂ /CuCl + free TPP	100
7	HDI poly-βCD Pd(OAc) ₂ /CuCl/TPP	100
8	MDI poly-βCD PdCl ₂ /CuCl	29
9	HDI poly-βCD PdCl ₂ /CuCl + free TPP	70
10	HDI poly-βCD PdCl ₂ /CuCl/TPP	100

^a = reactions carried out in DMF in the presence of TEA under conventional heating (70 °C for 3 hours); ^b = yields were determined by GC-MS.

Compared to poly-βCD/Pd/Cu nanoparticles, the catalytic activity of the free Pd(II) and Cu(I) salts (entries 1-4) is, in all cases, lower even in the presence of free TPP (entries 2, 4). Comparable results were obtained either with Pd(OAc)₂ or PdCl₂ as free salts (entries 1-4), while a difference was noticed when these salts were reticulated with the poly-βCD. Only Pd(OAc)₂ gave quantitative conversion in all cases (entries 5-7). The two cross-linkers investigated, the aromatic MDI and the aliphatic HDI, did not significantly influence the reaction rate. As expected, the favorable ligand stabilizing effect of TPP was a common feature. The biggest advantage of the poly-βCD system was the very low leaching of the metals and the total capture of TPP and the TPP-oxide formed. This greatly simplified the purification step and resulted in quantitative yields, without TPP and cation impurities in the products. In this context, it is noteworthy that the CD network serves as an efficient metal chelator which encapsulates the organic ligand as well. As seen before, this does not reduce the catalytic activity at all and could also find further applications in Pd- or Cu-based methodologies involving sensitive reagents. In a recent study, click chemistry has been used to coat polymer capsules with antibodies to target cancer cells. However, conventional alkyne-azide coupling in the presence of copper failed as clumps of antibody formed instead. Masking the copper with a chelator prevented the metal for interacting with the antibodies but still catalyzed the process²⁰.

With the aim of designing a fully sustainable eco-friendly procedure, two catalytic systems, HDI poly-βCD Pd(OAc)₂/CuCl/TPP (a) and HDI poly-βCD PdCl₂/CuCl/TPP (b) (entries 7 and 10 respectively in Table 1), were further used in water and glycerol, and the results were compared to those obtained in DMF (Table 2).

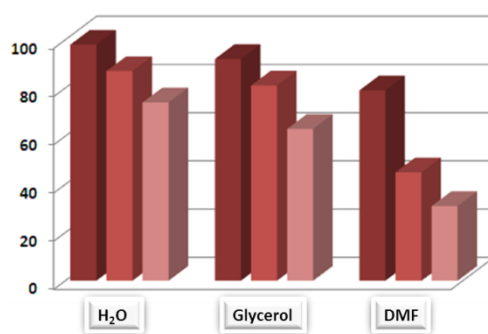
Both catalysts gave excellent results in water which shows that the addition of TBAB was absolutely useless or even deleterious as regards the purity of the product. Although a slight reduction in the reaction yield was observed in glycerol, higher product purity was achieved.

Table 2. Sonogashira reactions under conventional heating (70 °C for 3 hours).

Entry	Catalyst (2 %)	Solvent	Yield (%)
1	a	H ₂ O/TBAB	96
2	a	H ₂ O	98
3	a	glycerol	90
4	a	DMF	100
5	b	H ₂ O/TBAB	100
6	b	H ₂ O	100
7	b	glycerol	94
8	b	DMF	100

^a = HDI poly-βCD Pd(OAc)₂/CuCl/TPP; ^b = HDI poly-βCD PdCl₂/CuCl/TPP

Indeed no Glaser-type homocoupling was detected at all. In fact, reactions of terminal alkynes to diynes (Glaser products)²¹ are generated in high yields using Cu(I) as co-catalyst, especially in the presence of oxygen²². In stark contrast the poly-βCD catalysts described herein enable efficient and very clean reactions in glycerol and water even in an open vessel. Next, we selected HDI poly-βCD Pd/Cu/TPP nanoparticles to assess catalytic activity after recycling. Several tests were conducted in DMF, water and glycerol. Results are summarized in Figure 1 which shows that the most effective catalyst recycling occurred in water and glycerol.

**Figure 1.** Yield (%) in catalyst recycling (reaction in water, glycerol and DMF under stirring for 3 h at 70 °C).

Conclusions

The in situ polymerization of β-CD with diisocyanates in DMF under ultrasound irradiation was extremely fast and efficient. The presence of Pd/Cu salts and TPP in the reaction mixture leads to their stable inclusion in the CD-polymer net.

This guarantees excellent catalytic activity in Sonogashira reactions and very low metal leaching. Even more efficient was the inclusion of the TPP and the TPP-oxide formed during the reaction; in fact these two species were never detected in the crude reaction mixture. The use of water or glycerol as solvents rendered product purification much easier and also allowed the catalyst to be recycled via simple

filtration and washing. In these environmentally benign media, no oxidative homocoupling of alkynes (Glaser product) was detected. We have shown that catalyst reuse, particularly in water gave consistently good yields after three runs. The facile catalyst preparation together with the negligible leaching of metals and TPP/TPPO, and the use of green solvents unveil a truly sustainable protocol. New applications of these versatile catalysts in other carbon-carbon and carbon-heteroatom couplings are in the offing.

Experimental

Commercially available reagents and solvents were used without further purification unless otherwise noted. β -CD was kindly provided by Roquette (France). The sonochemical reactor used in the present work was developed at the University of Turin and designed for stringent reaction conditions¹⁷. All critical parameters (power, frequency, reaction temperature and composition of the modified atmosphere) were optimized. The eccentric rotation of the thermostatted reaction vessel around the horn axis and the alternative up and down excursion of the probe were key features for the success of polymerization reactions. GC-MS analysis were carried out with a gas chromatograph Agilent 6890 (Agilent Technologies - USA) fitted with a mass detector Agilent Network 5973 using a capillary column 30 m long, an i.d of 0.25 mm and a film thickness of 0.25 μ m. The metal content in solution was determined by ICP-MS on a Quadrupole-ICP-MS X Series II (Thermo Fisher Scientific) after the samples digestion in HNO₃ and aqua regia (1 HNO₃/3 HCl). The oxidation state of the adsorbed palladium or copper was measured by X-ray photoelectron spectroscopy (XPS) with a Quantum 2000 (PHI Co., Chanhassen, MN, USA) with a focused monochromatic Al K source (1486.7 eV) for excitation.

In a typical preparation of poly- β CD/Pd/Cu nanoparticles Pd(OAc)₂ (50 mg, 0.22 mmol) or PdCl₂ (50 mg, 0.28 mmol), CuCl (50 mg, 0.5 mmol), and β -CD (1 g, 0.78 mmol), were dissolved in DMF in (25 mL) under sonication in a thermostatted sonochemical reactor at room temperature. Hexamethylene diisocyanate (HDI) (1.4 mL, 8.7 mmol) or methylene diphenyl diisocyanate (MDI) (1.8 g, 7.19 mmol) was then added portion-wise and the reaction was kept under sonication at 60 °C (21.1 kHz, 60 W) for 30 min. The compact gel was crushed and washed with water (100 mL), acetone (100 mL), and methanol (100 mL). The product was filtered on a sintered glass Buchner funnel and dried overnight under vacuum at 75 °C, obtaining a brownish-green powder (2.23 g). Longer reaction times (90 min) were required when the reaction was carried out under simply magnetic stirring (silent conditions at the same temperature) and a much more irregular powder granulometry was recovered. The preparation of the catalyst with triphenylphosphine follows the same procedure with 2% mol TPP added to the reacting mixture.

The typical procedure of Sonogashira reaction employed *p*-iodoanisole (1 mmol), phenylacetylene (1 mmol), 0.5-2 % mol of poly- β CD/Pd/Cu nanoparticles (150 mg), triethylamine (2 mL) and when required TBAB (1 mmol), were dispersed in suitable solvents such as DMF, H₂O or glycerol (3 mL) and were stirred for 3 hours at 70 °C under argon. 10 mL of 0.1N H₂SO₄ were added to the reaction mixture and the products were extracted three times with 30 mL of EtOAc. For reactions in glycerol, the products were directly extracted with EtOAc (three times). The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. For reactions in DMF or H₂O, the catalyst was then filtered and washed successively with EtOAc, acetone and methanol, then dried at 75 °C overnight.

Overall conversions and yields were determined by GC-MS analysis.

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Notes and references

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